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EXAMINER

SKELDING, ZACHARY S

ART UNIT PAPER NUMBER

1644

DATE MAILED: 07/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/616,760	GELBOIN ET AL.	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 April 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-73 is/are pending in the application.
- 4a) Of the above claim(s) 1-12 and 27-73 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>November 28, 2003</u> | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1644

DETAILED ACTION

1. Applicant's amendment of July 9, 2003 has been entered.

Claims 1-73 are pending.

2. Applicant's election with traverse of Group II in the reply filed on April 25, 2006 is acknowledged. Applicant has traversed the restriction between Groups II and III on the grounds that the claimed binding agents compete for specific binding to the same antigens, i.e., the p450 2C9 allelic variants, and that there is no undue search burden.

This is not found persuasive because the antibody binding agents of Groups II and III differ in their epitopic specificities, meaning they bind to distinct structures and are therefore structurally distinct themselves. This is evident from the disclosure of the instant specification where MAb 763-15-5 (Group II) and MAb 763-15-20 (Group III) are distinguished by their antigen specificity (the former specifically recognizes p450 2C9 while the later recognizes 2C9 and 2C8); and their relative enzyme inhibitory activities: **MAb 763-15-20** has **no effect on the enzyme activity of two of the P450 2C9 alleles** and just a 10% affect on the third allele, while **MAb 763-15-5** inhibits the enzyme activity of **all three P450 2C9 alleles** by more than 75% (see instant specification, page 28, 1st and 2nd paragraphs and paragraph bridging pages 10-11)

Thus, these products are patentably distinct, and searching these inventions would impose an undue burden.

Therefore, the restriction requirement is maintained and made FINAL.

Should applicant continue to traverse on the grounds that these inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

3. Claims 13-26 are under examination as they read on a monoclonal antibody that competes with monoclonal antibody 763-15-5 for binding to human p450 2C9 allelic variants and specifically inhibits metabolism of phenanthrene.

Claims 1-12 and 27-73 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being directed to a non-elected invention.

Art Unit: 1644

4. Claims 13-26 are entitled to the benefit of priority as of the filing date of the parent of the instant application, USSN 09/469,655, filed **December 22, 1999**, as this is the claimed priority document which discloses MAb 763-15-5. If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the provisional application. Applicant is reminded that such priority for the instant limitation requires written description and enablement under 35 U.S.C. 112, first paragraph.

5. Applicant's IDS, filed November 28, 2003, is acknowledged and has been considered.

6. The first sentence of the instant specification should be amended to indicate that USSN 09/469,655 is now patented.

7. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

8. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

For example, ELIZA is misspelled on page 28, first paragraph.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

9. The abstract page of the instant specification begins with the heading, "Agents that bind..."; however, according to 37 C.F.R. § 1.72, the abstract must commence on a separate sheet, preferably following the claims, under the heading "Abstract" or "Abstract of the Disclosure."

Appropriate correction is required.

10. ATCC Deposit: Claims 13, 16, 23 and 24

It is apparent that the monoclonal antibodies, "MAb 763-15-5" and "MAb 292-2-3", produced by the ATCC PTA-1079 and ATCC HB-12645 hybridomas, respectively, are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines / hybridomas which produce these antibodies. See 37 CFR 1.801-1.809.

Art Unit: 1644

Given the amendment of July 9, 2003 to the instant specification, the conditions for the deposit of biological materials under 35 U.S.C. § 112, 1st paragraph, with respect to "MAb 763-15-5", produced by the ATCC PTA-1079 hybridoma, and "MAb 292-2-3", produced by the ATCC HB-12645 hybridoma, appear to have been met.

11. Claims 13-26 are rejected under **35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 13, 16, 23 and 24, and dependent claims thereof, are indefinite in the recitation of "MAb 763-15-5" and "MAb 292-2-3" because the characteristics of these molecules are not known. The use of "MAb 763-15-5" and "MAb 292-2-3" as the sole means of identifying the molecules with which the claimed binding agent competes renders the claim indefinite because "MAb 763-15-5" and "MAb 292-2-3" are merely laboratory designations which do not clearly define these antibodies, since different laboratories may use the same designations to define completely distinct biological materials.

Applicant is invited to amend the claim to indicate that ATCC PTA-1079 hybridoma produces MAb 763-15-5 and that ATCC HB-12645 hybridoma produces MAb 292-2-3, as disclosed on page 11 of the instant specification.

B. Claim 13, and dependent claims thereof, is further indefinite in the recitation of "inhibits 2C-catalyzed metabolism of phenanthrene by at least 50%." It is unclear if "2C" is meant to refer to all members of the 2C family of p450 enzymes, i.e., 2C9, 2C8, 2C19 etc., or only the p450 2C9 allelic variants recited in the claim.

C. Claims 15, 25 and 26 are indefinite in the recitation of "the enzyme activity of human cytochrome p450 allelic variant 2C9*2"; "the enzyme activity of human cytochrome p450 allelic variants 2C9*1 and 2C9*3"; and "the enzyme activity of human cytochrome p450 2C18", respectively. There is insufficient antecedent basis for these limitations in the instant claims, i.e., it is unclear if "the enzyme activity" refer to "metabolism of phenanthrene" as recited in claim 13 or metabolism of some other substrate, such as one of the "numerous drugs and non-drug xenobiotics" listed in the paragraph bridging pages 2-3 of the instant specification.

D. Claim 16 is indefinite in the recitation of "MAb 292-2-3 or a **binding fragment thereof**". It is unclear if a "binding fragment" means a fragment which must bind to the human cytochrome p450 2C9 allelic variants or a fragment which binds to something, *but not necessarily the human cytochrome p450 2C9 allelic variants*, such as a fragment of the Fc region which would bind to the Fc receptor but not the human cytochrome p450 2C9 allelic variants.

Art Unit: 1644

E. Claim 18-20, 23 and 24, and dependent claims thereof, are indefinite in the recitation of "the monoclonal antibody of claim 17" because claim 17 is drawn to a binding agent not a monoclonal antibody.

Applicant is invited to amend claims 18-20 and 23 to recite "the binding agent of claim 17" in place of "the monoclonal antibody of claim 17".

F. Claim 22 is indefinite in that it is drawn to a "procaryotic cell line" and depends from claim 21 which is drawn to a "eucaryotic cell line", which are mutually exclusive types of cell lines.

Applicant is invited to amend claim 22 so that it depends from claim 20.

G. Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 13-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A. Any "binding agent": Claims 13-15, 25 and 26

Claims 13-15, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the instant specification lacks a sufficient enabling description for any "binding agent" that competes with a monoclonal antibody MAb 763-15-5 for specific binding to the human cytochrome P450 2C9 allelic variants *and* upon binding, specifically inhibits a certain enzyme activity of said P450 2C9 allelic variants or another 2C family member, such as 2C18.

For the purposes of examination under 35 U.S.C. § 112, 1st paragraph and 35 U.S.C. § 102/103, claim 13, given its broadest reasonable interpretation consistent with the specification, will be considered as reading on any "binding agent" that competes with monoclonal antibody MAb 763-15-5 for its (MAb 763-15-5's) specific binding to all three "human cytochrome p450 2C9 allelic variants 2C9*1, 2C9*2 and 2C9*3" *and* that specifically inhibits 2C-catalyzed metabolism of phenanthrene by at least 50%, wherein, "2C-catalyzed metabolism" will be interpreted as comprising 2C9*1, 2C9*2 and 2C9*3 catalyzed metabolism.

Art Unit: 1644

Thus, “MAb 763-15-5” of claim 13 specifically binds p450 2C9 allelic variants 2C9*1, 2C9*2 and 2C9*3 **but not other cytochrome P450s**, while the “**binding agents**” of claim 13 includes those which, while competitive with monoclonal antibody MAb 763-15-5 for binding to 2C9*1, 2C9*2 and 2C9*3 **and** while being able to “inhibit 2C9*1, 2C9*2 and 2C9*3 catalyzed metabolism of phenanthrene by at least 50%”, do not themselves necessarily specifically bind to the human cytochrome p450 2C9 allelic variants 2C9*1, 2C9*2 and 2C9*3.

The instant specification discloses how to prepare monoclonal antibodies that specifically bind PF450 2C9*2, and discloses a particular anti-2C9 antibody species, MAb 763-15-5, which **specifically binds** human cytochrome p450 allelic variants 2C9*1, 2C9*2 and 2C9*3, **and** upon binding, **specifically inhibits** p450 2C9*1, 2C9*2 and 2C9*3 enzyme activities. (See specification paragraphs bridging pages 10-11, page 25, second paragraph, page 28, 1st-3rd paragraphs).

However, the instant specification does not provide sufficient guidance and direction as to how to make **any** “binding agent” such as “non-antibody binding agents...include[ing] polypeptides, beta-turn mimetics, polysaccharides, phospholipids, hormones, prostaglandins, steroids, aromatic compounds...” (as disclosed on page 18, lines 18-23 of the instant specification) with the claimed limitations.

The publication of Gelboin et al. (Trends Pharmacol Sci. 1999 Nov;20(11):432-8) illustrates the difficulty of creating, for example, chemical “binding agents” with the claimed limitations. Gelboin et al. teaches that, in general, P450 inhibitors are often **selective**, i.e., recognize multiple members of a P450 family, for example 2C9, 2C8 and 2C19, **rather than specific** for a particular member of the P450 family, such as the claimed P450 2C9 allelic variants (See page 434, 1st paragraph).

Moreover, Gelboin et al. teaches that, in contrast to monoclonal antibodies, chemical inhibitors have different effects on P450 enzymes **dependent on their concentration**.

Thus, undue experimentation would be required for one of skill to create a chemical inhibitor of P450 2C9 which could (1) compete with MAb 763-15-5 for binding to 2C9 in the presence of other 2C family members like 2C8 and 2C19 due to the lack of **specificity** and (2) specifically inhibit 2C9 catalysis due to the **concentration dependence** of the enzyme inhibitory activities.

B. Competes with MAb 763-15-5 for “specific binding” under all conditions: Claims 13-26

Claims 13-26 are rejected under 35 U.S.C. 112, first paragraph, because the instant specification lacks a sufficient enabling description for an isolated binding agent

Art Unit: 1644

that competes with a monoclonal antibody MAb 763-15-5 for “specific binding” **under all conditions**.

According to the instant specification MAb 763-15-5 specifically binds human cytochrome p450 allelic variants 2C9*1, 2C9*2 and 2C9*3 when binding is measured by ELISA; however, MAb 763-15-5 does **not** bind human cytochrome p450 allelic variants 2C9*1, 2C9*2 and 2C9*3 in an immunoblot (see figures 8 and 10, and page 28, 1st and 2nd paragraphs).

Thus, one of skill in the art would not know how to assess a binding agents ability to compete with MAb 763-15-5 for binding to human cytochrome p450 allelic variants 2C9*1, 2C9*2 and 2C9*3 **under all conditions**, such as when the cytochrome P450 target is immobilized on an immunoblot, because 763-15-5 does not bind cytochrome P450 under these conditions.

C. MAb 292-2-3 as the “binding agent”: Claim 16

Claim 16 is rejected under 35 U.S.C. 112, first paragraph, because the instant specification lacks a sufficient enabling description for the use of **MAb 292-2-3** to compete with monoclonal antibody MAb 763-15-5 for specific binding to **all three** “human cytochrome p450 2C9 allelic variants **2C9*1, 2C9*2 and 2C9*3**”.

According to the instant specification **MAb 292-2-3** binds human cytochrome p450 allelic variant 2C9*2 but does not bind **2C9*1 or 2C9*3**. See instant specification, in particular, Figures 4 and 5.

Thus, one of skill in the art would not be able to use **MAb 292-2-3** to compete with monoclonal antibody MAb 763-15-5 for specific binding to **all three** “human cytochrome p450 2C9 allelic variants **2C9*1, 2C9*2 and 2C9*3**” as MAb 292-2-3 does not bind 2C9*1 or 2C9*3.

D. **any** “three CDR regions”: Claim 24

Claim 24 recites, “The monoclonal antibody of claim 17, wherein the light chain variable domain comprises **three CDR regions** from the light chain of a monoclonal antibody MAb 763-15-5...”

For the purposes of examination claim 24, given its broadest reasonable interpretation consistent with the specification, will be considered as reading on a light/heavy chain variable domain comprising **any three CDR regions** from the light/heavy chain of monoclonal antibody MAb 763-15-5, including **for example**, a light/heavy chain variable domain comprising **three copies of CDR1** from the light/heavy chain of monoclonal antibody MAb 763-15-5.

Art Unit: 1644

Claim 24 is rejected under 35 U.S.C. 112, first paragraph, because the instant specification lacks a sufficient enabling description for a monoclonal antibody wherein the light chain variable domain comprises any “three CDR regions” from the light chain/heavy chain of MAb 763-15-5.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin.

For example, Janeway et al. teach that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (See Janeway et al., Immunobiology, 5th Ed., Garland Science, pp. 94-105 (2001)).

Thus, undue experimentation would be required for one of skill to create an antibody comprising any “three CDR regions” from the light chain/heavy chain of MAb 763-15-5.

E. “80% sequence identity”: Claim 23

Claim 23 is rejected under 35 U.S.C. 112, first paragraph, because the instant specification lacks a sufficient enabling description for a monoclonal antibody “binding agent” that is 80% identical to MAb 763-15-5 which retains the biological activities put forth in claim 13.

The instant specification discloses that the anti-P450 2C9 antibodies can undergo non-critical amino acid substitutions and other changes in the both the variable and constant regions without loss of specificity or effector function (see instant specification, page 18, 1st paragraph).

However, the scope of the claimed monoclonal antibody “binding agent” that is 80% identical to MAb 763-15-5 is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of amino acid sequences broadly encompassed by the claimed invention. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a antibody while still retaining similar biological activity or structural specificity requires a knowledge of and guidance with regard to which amino acids in the protein’s sequence, if any, are tolerant of modification and which are

Art Unit: 1644

conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function.

Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as taught by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979, citation number 25 on the IDS submitted November 28, 2003). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Moreover, as taught by Chien et al., (Proc Natl Acad Sci U S A. 1989 Jul;86(14):5532-6), changing a single amino acid residue **outside and distant from the active site**, is also capable of completely eliminating antigen binding(see Chien, page 5536, 3rd paragraph). Chien concludes, "Our results and observations by others of substitutions in JH1 and in JH3 and JH4 suggest that residues distant from the binding site may play an important role in the specificity and affinity of the antigen-binding site." (see Chien, page 5536, 3rd paragraph).

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

14. Claims 13-15, 17-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the art that the inventor(s), at the time of the application was filed, had ***possession*** of the claimed invention.

As stated above, for the purposes of examination under 35 U.S.C. § 112, 1st paragraph and 35 U.S.C. § 102/103, claim 13, given its broadest reasonable interpretation consistent with the specification, will be considered as reading on **any** "binding agent" that competes with monoclonal antibody MAb 763-15-5 for **its (MAb 763-15-5's) specific binding to all three** "human cytochrome p450 2C9 allelic variants 2C9*1, 2C9*2 and 2C9*3" ***and*** that specifically inhibits 2C-catalyzed metabolism of phenanthrene by at least 50%, wherein, "2C-catalyzed metabolism" **will be interpreted as comprising 2C9*1, 2C9*2 and 2C9*3 catalyzed metabolism**.

Art Unit: 1644

The instant claims are drawn to “binding agents” which “compete with monoclonal antibody MAb 763-15-5 for specific binding to the human cytochrome p450 2C9 allelic variants 2C9*1, 2C9*2, and 2C9*3, and that specifically inhibits 2C-catalyzed metabolism of phenanthrene by at least 50%,” wherein the “binding agent” is, for example:

- *any* “binding agents” including non-antibody binding agents such as chemicals (Claims 13-15, 25 and 26);
- *any* monoclonal antibody or cell line producing said monoclonal antibody (Claims 17-22); or
- *any* monoclonal antibody that is 80% identical to the light/heavy chain variable region of MAb 763-15-5 as well as any monoclonal antibody comprising *any* three variable domains from 763-15-5 (Claims 23 and 24).

There is insufficient written description in the specification as-filed for the above recited “binding agents”. The claimed “**binding agents**” lack a common structure essential for their function, and the claims do not require any particular structure basis be shared by the instant “**binding agents**”. The genus of the “**binding agents**” are therefore extremely large.

The instant specification discloses just a single species of “binding agent” that can compete with MAb 763-15-5 for binding to all three PF450 alleles, i.e., 2C9*1, 2C9*2 and 2C9*3, AND which also inhibits 2C9*1, 2C9*2 and 2C9*3 catalyzed metabolism of phenanthrene by at least 50%: MAb 763-15-5 itself (see instant specification, for example, figures 8 and 11).

It does not appear based upon the disclosure of MAb 763-15-5 alone that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the extensive variation permitted within the genus of “**binding agents**”.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. (See Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, especially page 1106 3rd column). A “representative number of species” means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. MPEP 2163 II.A.3a.ii.

Art Unit: 1644

“Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention.” Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997).

The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 1115).

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

16. Claims 13-15 and 25 are rejected under 35 U.S.C. § 102(a) as being anticipated by Tang et al. (Chem Res Toxicol. 1999 Feb;12(2):192-9)(See entire document).

Tang teaches an isolated binding agent that competes with a monoclonal antibody MAb 763-15-5 for specific binding to the human cytochrome p450 2C9 allelic variants, in particular an anti-P450 2C9 antibody, (See entire document, in particular materials and methods, page 193).

Tang further teaches that the anti-P450 2C9 antibody (which is a rabbit polyclonal antibody, see Lasker et al., Arch Biochem Biophys. 1998 May 1;353(1):16-28), specifically inhibits p450 2C-catalyzed metabolism of a P450 substrate, in particular diclofenac, by at least 70% (See, for example, results pages 193-197, in particular Table 2).

Given that MAb 763-15-5 of the instant invention specifically inhibits p450 2C-catalyzed metabolism of **phenanthrene AND diclofenac** by at least 70% (as disclosed in the paragraph bridging pages 10-11 of the instant specification), the antibodies of Tang which specifically inhibits p450 2C-catalyzed metabolism of diclofenac by at least 70% *inherently* competes with MAb 763-15-5 for binding to P450 2C9 alleles and inhibits p450 2C-catalyzed metabolism of phenanthrene by at least 70%.

Since the Office does not have a laboratory to test the anti-P450 2C9 antibody of Tang, it is applicant's burden to show that the reference antibody **does not** compete with monoclonal antibody MAb 763-15-5 for specific binding to the human cytochrome p450

Art Unit: 1644

2C9 allelic variants 2C9*1, 2C9*2, and 2C9*3, and/or that the reference antibody **does not** specifically inhibit 2C-catalyzed metabolism of phenanthrene by at least 70%. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

18. Claims 13-15, 17-21 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mei et al. (J Pharmacol Exp Ther. 1999 Nov;291(2):749-59) in view of Tang et al. (Chem Res Toxicol. 1999 Feb;12(2):192-9) and Melvin et al. (U.S. Patent No. 6,242,203)(See entire documents).

Mei teaches that monoclonal antibodies **inhibitory** to individual cytochrome P450 molecules (CYPs) are ideally suited for CYP investigation, and due to their properties "a library of inhibitory MAbs would be valuable the characterization of the multiple forms of CYP involved in the metabolism of a drug..." (See entire document, in particular introduction, pages 749-750). Mei also teaches the production of mouse monoclonal antibody and eukaryotic cell lines for producing monoclonal antibodies (See entire document, in particular materials and methods, pages 750-751).

The claimed invention differs from the reference teaching in the recitation of an anti-P450 2C9 antibody or antigen binding fragment thereof, including Fab, that competes with monoclonal antibody MAb 763-15-5 for specific binding to the human cytochrome p450 2C9 allelic variants, and that specifically inhibits 2C-catalyzed metabolism of phenanthrene by at least 50%.

Tang teaches anti-P450 2C9 antibody (which is a rabbit polyclonal antibody, see Lasker et al., Arch Biochem Biophys. 1998 May 1;353(1):16-28), which specifically inhibits p450 2C-catalyzed metabolism of diclofenac by at least 70% (See, for example, results pages 193-197 and Table 2).

Given that MAb 763-15-5 of the instant invention specifically inhibits p450 2C-catalyzed metabolism of **phenanthrene AND diclofenac** by at least 70% (as disclosed in the paragraph bridging pages 10-11 of the instant specification), the antibodies of Tang which specifically inhibits p450 2C-catalyzed metabolism of diclofenac by at least 70% intrinsically competes with MAb 763-15-5 for binding to P450 2C9 alleles and inhibits p450 2C-catalyzed metabolism of phenanthrene by at least 70%.

Art Unit: 1644

Tang further teaches that the use of anti-P450 2C9 antibodies to study P450 2C9 metabolism of diclofenac is of interest because metabolism of this drug can cause liver injury. (See entire document, in particular Introduction, pages 193-194).

Melvin teaches antigen binding fragments of antibodies, including Fab fragments, that bind to cytochrome P450 1B1 (See entire document, column 2, 6th paragraph).

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the teaching of Mei and Tang to practice the claimed invention because, as taught by **Mei**, monoclonal antibodies *inhibitory* to individual cytochrome P450 molecules (CYPs) are valuable for the characterization of the multiple forms of CYP involved in the metabolism of drugs, and as taught by **Tang**, *anti-P450 2C9 inhibitory antibodies* are of particular interest for studying the medically interesting P450 2C9 metabolism of the drug *diclofenac* (said antibodies intrinsically competing with MAb 763-15-5 and inhibiting the p450 2C-catalyzed metabolism of phenanthrene by at least 70%).

Furthermore, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of **Mei, Tang and Melvin** to arrive at the claimed antibody fragments including *Fab fragments* since Melvin teaches such antibody fragments can be used in, addition to traditional antibodies, to detect a particular cytochrome p450 enzyme, 1B1.

Given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Art Unit: 1644


19. No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 9:00 a.m. - 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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